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(54) The effect of a combination of a beta-adrenergic agonist and certain histamine H1- and/or H2-receptor blockers on gastrointestinal injury produced by nonsteroidal anti-inflammatory compositions.

(57) Pharmaceutical composition and process for administering NSAIDs with a combination of beta-adrenergic agonist and certain H₁-and H₂-receptor blockers which protect against injury to the gastrointestinal tract.

EP 0 321 613 A1

The Effect of a Combination of a Beta-Adrenergic Agonist and Certain Histamine H₁- and/or H₂-Receptor Blockers on Gastrointestinal Injury Produced by Nonsteroidal Anti-Inflammatory Compositions.

This invention relates to nonsteroidal anti-inflammatory compositions containing, as protectants against gastrointestinal injury caused by said nonsteroidal anti-inflammatory drugs (hereinafter referred to as NSAID), combinations of a beta-adrenergic agonist and histamine-receptor blockers selected from the group consisting of H₁- and H₂-blockers and mixtures thereof. The compositions of this invention are useful in treating conditions and symptoms that are classically treated by the administration of NSAIDs, e.g., headache pain, pain and inflammation associated with arthritis and other systemic diseases, elevated body temperatures, etc.

Aspirin and other NSAIDs have long been the most popular drugs for the management of pain, inflammation and fever in individuals. However, one of the drawbacks is the gastrointestinal injury and/or bleeding that sometimes accompanies their administration. This becomes a particular problem where large and sustained doses of NSAIDs must be given to control the symptoms, as for example, in the case of the management of arthritis.

It has now been found that NSAID-induced gastrointestinal injury can be significantly reduced when a combination of a beta-adrenergic agonist and a histamine-receptor blocker selected from the group consisting of histamine H₁-, H₂-receptor blockers and mixtures thereof is administered concurrently with said NSAID.

As pointed out in U.S. Patent 4996571, H₁- and H₂-receptor blockers form two well-known and distinct classes of pharmacologically active drugs that serve as blocking agents for histamine at H₁- and H₂-receptor sites, respectively. Histamine-receptor sites have been differentiated on the basis of the classes of antihistamines that can serve to block these sites. The fact that a drug is identified as an antihistamine does not necessarily mean that it will be effective in blocking all the known histamine-receptor sites but may, in fact, be selective so that it will act at one site e.g. H₁ site but not at another, e.g., H₂ site.

It has been reported in prior art that H₂-receptor blocking agents protect against aspirin-induced lesions in certain laboratory animals. One such study is reported in *Gastroenterology* Vol. 88, No. 5 part 2. p. 1344. It has also been reported that cyproheptadine has been evaluated as a protectant against aspirin-induced gastrointestinal injury (*Indian J. Med. Res.* 1980, 71, p. 926-32). Although cyproheptadine may have some H₁-receptor antagonist properties, it does not act exclusively at the H₁-receptor sites but rather acts predominantly to block the serotonin receptor sites. (*Goodman and Gilman, "The Pharmacological Basis of Therapeutics."* Seventh Edition, p. 634).

Aside from the above, the present invention has further significant distinctions from the teachings in the Indian Journal. For one thing in this reference the aspirin and the cyproheptadine are not coadministered, as would be the case in the present invention. Furthermore, the treatment in this reference with cyproheptadine is reported as not modifying the gastric acidity and is contrary to the observations made in connection with the present invention. Moreover, in the Indian, reference the cyproheptadine was administered by intraperitoneal injection prior to the intragastric administration of the aspirin. In contrast, the compositions of the present invention lend themselves to oral administration, at which time the NSAID and the combination H₁- and H₂-receptor blockers are coadministered.

Moreover, there is nothing in the prior art cited above to suggest the essential feature of the present invention, namely the use of the combination of a beta-adrenergic agonist along with the histamine H₁- and/or H₂-receptor blockers.

Numbers of H₁-and H₂-receptor blockers are known in the prior art which are useful for the purposes of the present invention. By way of illustrating the H₁-receptor blockers that may be employed herein, mention may be made of the following: ethanolamines (e.g. diphenhydramine or its hydrochloride salt; carbinoxamine or its maleate salt); ethylenediamines (e.g. tripeleannamine or its hydrochloride or citrate salts); alkylamines (e.g. chlorpheniramine or its maleate salt, brompheniramine or its maleate salt); and piperazines (e.g. hydroxyzine or its hydrochloride or pamoate salts, cyclizine or its hydrochloride or lactate salts, etc.). To exemplify the H₂-receptor blockers that may be advantageously used in the practice of this invention, the following are given: cimetidine, ranitidine, famotidine, etc.

The H₁-and H₂-receptor blockers may be used in the form of their bases or in the form of their pharmaceutically acceptable salts. When employed as salts, these will usually be acid-addition salts wherein the acid portion may be hydrochloric, maleic, ascorbic, citric, pamoic, lactic, tartaric, etc.

The beta-adrenergic agonists also form a fairly well-defined class of pharmaceutically effective com-

pounds that are characterized by the fact that they act by stimulating beta-adrenergic receptor sites. These receptor sites are of two types, referred to as the β_1 , and β_2 sites. Beta-adrenergic agonists may act on one or the other or on both types of sites.

Numerous beta-adrenergic agonists are known in the prior art which are useful for the purposes of this invention. Of special interest is terbutaline which is a β_2 agonist. By way of illustrating other beta-adrenergic agonists that may be employed herein, the following are given: isoproterenol, metaproterenol, and albuterol. All of these may be employed as such or as pharmaceutically acceptable salts.

The NSAIDs also form a well-known class of drugs that are anti-inflammatory analgesics. These have the common property of inhibiting the formation of prostaglandins which have a protective effect on the gastrointestinal mucosa. See Goodman and Gilman "The Pharmacological Basis for Therapeutics" 7th Edition, p. 678. It is because of this inhibiting effect that the oral administration of drugs of this class tends to result in gastrointestinal injury and/or bleeding and is at least part of the problem that the present invention seeks to reduce or eliminate.

Numbers of NSAIDs are known in the prior art to which the present invention has application. The most commonly known group is the salicylates of which aspirin is the prime example. A further group of NSAIDs that has utility in connection with the instant invention is the propionic acid derivatives. Included in this group are, for example, ibuprofen and naproxen. Still a further group of NSAIDs, employable herein, is the fenamates and compounds closely related to them structurally. These may be illustrated by such compounds as mefenamic acid, meclofenamate sodium, and diclofenac and its sodium salt. Also belonging to the class NSAIDs with which the present invention is concerned are the indole derivatives (e.g. indomethacin); pyrrole alkanoic acid derivatives (e.g. tolmetin); pyrazalone derivatives (e.g. phenylbutazone); oxicams (e.g. piroxicam); etc.

It is contemplated that in the practice of the present invention the NSAID, the beta-adrenergic agonist, and the histamine-receptor blocker or blockers will be administered concurrently in a convenient product form. The essential ingredients of such products will be the histamine H₁-and/or H₂-receptor blocker, the beta-adrenergic agonist, and the NSAID. Over and above this, these products may also contain other ingredients which will, to a large extent, depend upon the particular dosage form of the product, e.g., tablets, capsules, powders, suspensions, etc.

The quantity of H₁-receptor blocker that will be contained in the composition of this invention may vary somewhat. All that is required is that an effective amount be present so that the H₁-receptor blocker can make its contribution as a protectant against NSAID-induced gastrointestinal injury.

Similarly the quantity of H₂-receptor blocker in the present composition may also vary. Again, all that is required is that the amount employed be an effective quantity that will enable the H₂-receptor blocker to play its part as protectant.

The quantity of beta-adrenergic agonist that will be contained in the present composition may vary somewhat. Again, all that is required is that it be present in sufficient amount to function as a protectant for NSAID-induced gastrointestinal injury when employed with the other active ingredients that form part of the composition of this invention.

The NSAID will be contained in the composition of this invention at concentrations at which it is generally found in therapeutic NSAID compositions intended for oral administration. This will usually be a pharmaceutically acceptable analgesic/anti-inflammatory dose.

The quantitative relationship of the NSAID, the beta-adrenergic agonist, and the histamine H₁-and/or H₂-receptor blockers contained in the products of the present invention may be expressed in terms of the average daily dose of these ingredients, e.g., mg/kg of body weight/day. These relationships are set forth in Table I below, the general and preferred ranges being specified therein. The ranges specified for the histamine H₁-and H₂-receptor blockers are those that apply when the H₁ or H₂ blocker is employed. When a combination of the H₁ and H₂ blocker is utilized the amount of each contained in the product will be adjusted.

Table I

Ingredient	General Range		Preferred Range	
	low	high	low	high
NSAID	10 mg/kg/day - 100 mg/kg/day		15 mg/kg/day - 75 mg/kg/day	
Beta-Adrenergic Agonist	0.3 ug/kg/day - 500 mg/kg/day		0.01 mg/kg/day - 10 mg/kg/day	
Histamine H ₁ -Receptor Blocker (when employed)	2.5 ug/kg/day - 500 mg/kg/day		100 ug/kg/day - 50 mg/kg/day	
Histamine H ₂ -Receptor Blocker (when employed)	10 ug/kg/day - 1 g/kg/day		0.01 mg/kg/day - 10 mg/kg/day	

The unit dosage forms for the present invention will be formulated for convenient oral administration. The range of the quantities of each ingredient is set forth in Table II below. The ranges specified for the histamine H₁-and H₂-receptor blockers are those that apply when the H₁ blocker or the H₂-blocker is employed. When a combination of the H₁ and H₂ blockers is utilized the amount of each in the product will be adjusted.

Table II

INGREDIENT	UNIT DOSAGE mg/dose
NSAID	200mg - 600 mg
Beta-Adrenergic Agonist	0.7 mg - 70 mg
Histamine H ₁ - Receptor Blocker (when used)	0.01 mg - 70 mg
Histamine H ₂ - Receptor Blocker (when used)	0.5 mg - 350 mg

Depending upon the dosage form employed, the products of this invention may also contain other adjuvants that may be useful in formulating or administering the particular dosage form. Thus for example, when administered as a tablet, the products of this invention may also contain lubricants, excipients, binding agents, disintegrating agents, flavoring agents, etc. In addition, these products may also contain other pharmaceutically active ingredients such as: decongestants, analgesic adjuvants, expectorants, antitussives, diuretics, other analgesics, other anti-inflammatory agents, antipyretics, anti-rheumatics, anti-oxidants, vasodilators, smooth musclerelaxants, skeletal muscle relaxants, bronchodilators, vitamins, trace minerals, amino acids, and biological peptides.

As indicated above, the products of the present invention may assume the form of tablets. However, they may also be formulated as caplets or be in powdered or granular form contained in edible capsules such as gelatin capsules. The present products may also be made up as suspensions or solutions of the above ingredients in a suitable liquid medium or as powders packaged in suitable paper envelopes.

The following examples are given to further illustrate the present invention. It is to be understood, however, that this invention is not limited thereto.

Example 1

Aspirin 325 mg

Diphenhydramine hydrochloride 16.67 mg

The above ingredients are mixed in powdered or granular form and loaded into gelatin capsules.

Example 2

- Aspirin 325 mg
 5 Ranitidine hydrochloride 3.33 mg
 Prepared as described in Example 1.

Example 3

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- Aspirin 325 mg
 Metaproterenol sulfate 0.83 mg
 Prepared as described in Example 1.

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Dosage:

- Two capsules every 4 hours as needed. Do not exceed 8 capsules in 24 hours or give to children 12 or
 20 under, unless directed by a physician.

The following experiments were carried out to test the effectiveness of the combination of beta-adrenergic agonists with histamine H₁- or H₂-receptor blockers in protecting the stomach against NSAID-induced gastrointestinal injury. In these studies the histamine H₁-receptor blocker employed was diphenhydramine and it was used in the form of its HCl salt. The histamine H₂-receptor blocker utilized was
 25 ranitidine also employed in the form of its HCl salt. The beta-adrenergic agonist, exemplary of the present invention that was used in this test, was terbutaline. This was employed as the base.

A standard dose of 975 mg of aspirin is administered orally to obtain a benchmark for gastrointestinal injury. The histamine H₁- and H₂-receptor blockers and the beta-adrenergic agonists were tested separately along with the standard dose of 975 mg of aspirin for purposes of comparison with the irritation
 30 results obtained from the combination of the beta-adrenergic agonist with the histamine H₁- or H₂-receptor blocker when also administered with the standard test dose of 975 mg of aspirin.

The stomach lining of dogs is examined endoscopically and rated as to the degree of injury. The results are summarized in the tables following the description of the methodology which is given immediately below.

35 All test formulations are prepared on the day of the tests. The capsules are placed in the back of the dog's throat. A stomach catheter, with funnel attached, is positioned in the dog's stomach and 50 ml of deionized water is administered.

Healthy adult beagle dogs of either sex are selected for testing. Dogs are housed individually in stainless steel cages with grid floors to allow excreta to pass through. Room temperature in the holding
 40 rooms and test laboratories is maintained between 65° F and 85° F and relative humidity between 30% and 80%. Room lights remain on from 6:00 AM to 4:00 PM.

Each dog is trained to stand in a stanchion with sling support and to accept a bit tied in its mouth. A gastroscope is then passed through the bit into the dog's stomach. This training requires ten days to two weeks in most dogs.

45 To determine whether a dog is suitable for test purposes, its stomach is examined for a normal mucosa, and its gastric responsiveness to NSAID is evaluated (as under Test Procedure). An acceptable dog must have a gastric irritation score of 5 or greater, in the antrum 2 hours after dosage.

Food is withheld from test dogs for 24 hours before the test and during the test and water is allowed ad lib. The dogs are moved into a holding area away from the kennel. Fasted dogs of either sex are examined
 50 gastroscopically to ensure that their stomachs have normal healthy mucosal linings. The dogs are dosed orally with test formulations, which are flushed into their stomachs with 50 ml of deionized water. They are then re-examined two and four hours later for gastric petechiae and other signs of bleeding according to the following scale:

- 0 = uniform, pale to dark pink mucosa
- 55 1 = darker pink or blotchy mucosa
- 2 = petechiae and/or light red streaks
- 3 = few small lesions
- 4 = many or connected small lesions (striations)

5 = few large lesions

6 = many large lesions

7 = massive hemorrhagic damage

Severity of injury for each treatment and at each time is calculated as the mean gastric irritation score.

5 In addition to endoscopic observation of the gastric mucosa of each dog, a qualitative description of gastric fluid is recorded and a pH measurement is made of the gastric fluid. All of these are done 2 hours after administration of the test product.

A base line is established by measuring the various parameters after the administration of 975 mg of aspirin by itself. The resting normal stomach has an irritation score of 0 and a pH of 5 to 5.5. Aspirin 10 produces injury which scores at approximately 5.6 after 2 hours and the gastric pH at this time is about 3.1.

Table III

Nonsteroidal Anti-inflammatory Compositions Protected Against Gastrointestinal Injury with a Combination of Certain Beta - Adrenergic Receptor Agonists and Histamine H ₁ -Receptor Blocker:			
Data Summary			
		2-Hour Data	
		(N)	Irritation Score
	Aspirin 975 mg	8	5.5
25	Terbutaline 1.25 mg + Aspirin 975 mg	4	4.0
	" 2.50 mg + Aspirin 975 mg	4	2.0
	" 5.00 mg + Aspirin 975 mg	8	1.4
	" 10.0 mg + Aspirin 975 mg	5	1.2
	Diphenhydramine 12.5 mg + Aspirin 975 mg	4	5.5
30	" 25.0 mg + Aspirin 975 mg	4	5.75
	" 50.0 mg + Aspirin 975 mg	4	4.0
	Terbutaline 2.5 mg + Diphenhydramine 50 mg + Aspirin 975 mg	4	4.50
	Terbutaline 5.0 mg + Diphenhydramine 25 mg + Aspirin 975 mg	4	1.75
	Terbutaline 5.0 mg + Diphenhydramine 50 mg + Aspirin 975 mg	4	0.0
			5.4

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Table IV

5	<p style="text-align: center;">Nonsteroidal Anti-inflammatory Composition Protected Against Gastrointestinal Injury with a Combination of Certain Beta-Adrenergic Agonists and Histamine H₂-Receptor Blockers.</p>			
10	<p style="text-align: center;">Data Summary</p>			
15	<p style="font-size: small;">Aspirin 975 mg Terbutaline 1.25 mg + Aspirin 975 mg " 2.5 mg + Aspirin 975 mg " 5.0 mg + Aspirin 975 mg " 10.0 mg + Aspirin 975 mg Ranitidine 10 mg + Aspirin 975 mg " 20 mg + Aspirin 975 mg .50 mg + Aspirin 975 mg Terbutaline 5 mg + Ranitidine 10 mg + Aspirin 975 mg Terbutaline 5 mg + Ranitidine 5 mg + Aspirin 975 mg Terbutaline 2 mg + Ranitidine 5 mg + Aspirin 975 mg</p>	2-Hour Data		
20		(N)	Irritation Score	pH
25		8	5.5	3.3
		4	4.0	2.9
		4	2.0	3.8
		8	1.43	4.0
		5	1.2	4.6
		6	3.50	5.3
		8	1.88	5.9
		6	0.67	6.1

Claims

30. 1. A nonsteroidal anti-inflammatory composition having reduced potential for gastrointestinal injury comprising an anti-inflammatory amount of a nonsteroidal anti-inflammatory agent and a protective amount of a protectant comprising a beta-adrenergic agonist and a histamine receptor blocking component selected from the group consisting of histamine H₁-receptor blockers, and histamine H₂-receptor blockers, and a combination of histamine H₁- and H₂-receptor blockers.
35. 2. A composition according to claim 1, wherein said nonsteroidal anti-inflammatory agent is aspirin or ibuprofen.
3. A composition according to either of claims 1 and 2 wherein said beta-adrenergic agonist is terbutaline or a pharmaceutically acceptable salt thereof and said histamine H₁-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof.
40. 4. A composition according to any one of claims 1 to 3 wherein the amount of each ingredient present is sufficient to provide an average daily dose for the various ingredients as follows :
- (a) said nonsteroidal anti-inflammatory agent; from about 10 mg/kg/day to about 100 mg/kg/day,
 - (b) said beta-adrenergic agonist; from about 0.30 ug/kg/day to about 500 mg/kg/day,
 - (c) said histamine H₁-receptor blocker; from about 2.5 ug/kg/day to about 500 mg/kg/day.
45. 5. A composition according to any one of claims 1 to 3 wherein the amount of each ingredient present is sufficient to provide an average daily dose for the various ingredients as follows:
- (a) said nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day,
 - (b) said beta-adrenergic agonist; from about 0.01 mg/kg/day to about 10 mg/kg/day;
 - (c) said histamine H₁-receptor blocker; from about 0.1 mg/kg/day to about 50 mg/kg/day.
50. 6. A composition according to any one of claims 1 to 3 in unit dosage form containing the ingredients in the following amounts per unit dose:
- (a) said nonsteroidal anti-inflammatory agent; from about 200 mg to about 600 mg;
 - (b) said beta-adrenergic agonist; from about 0.7 mg to about 70 mg;
 - (c) said histamine H₁-receptor blocker; from about 0.01 mg to about 70 mg.

7. A composition according to either of claims 1 and 2 wherein said beta-adrenergic agonist is terbutaline or pharmaceutically acceptable salt thereof and said histamine H₂-receptor blocker is ranitidine or a pharmaceutically acceptable salt thereof.
8. A composition according to any one of claims 1, 2 or 7 wherein the amount of each ingredient present is sufficient to provide an average daily dose for the various ingredients as follows:
- (a) said nonsteroidal anti-inflammatory agent; from about 10 mg/kg/day to about 100 mg/kg/day,
 - (b) said beta-adrenergic agonist; from about 0.30 ug/kg/day to about 500 mg/kg/day,
 - (c) said histamine H₂-receptor blocker; from about 10ug/kg to about 1 g/kg/day.
10. 9. A composition according to any one of claims 1, 2 or 7 wherein the amount of each ingredient present is sufficient to provide an average daily dose for the various ingredients as follows :
- (a) said nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day,
 - (b) said beta-adrenergic agonist; from about 0.01 mg/kg/day to about 10 mg/kg/day,
 - (c) said histamine H₂-receptor blocker; from about 0.01 mg/kg/day to about 10 mg/kg/day.
15. 10. A composition according to any one of claims 1, 2 or 7 in unit dosage form containing the ingredients in the following amounts per unit dose:
- (a) said nonsteroidal anti-inflammatory agent; from about 200 mg to about 600 mg,
 - (b) said beta-adrenergic agonist; from about 0.7 mg to about 70 mg,
 - (c) said histamine H₂-receptor blocker; from about 0.5 mg to about 350 mg.

Claims for the following contracting States: ES, GR

25. A method of preparing a nonsteroidal anti-inflammatory composition having reduced potential for gastrointestinal injury comprising combining an anti-inflammatory amount of a nonsteroidal anti-inflammatory agent and a protective amount of a protectant comprising a beta-adrenergic agonist and a histamine receptor blocking component selected from the group consisting of histamine H₁-receptor blockers, and histamine H₂-receptor blockers, and a combinations of histamine-H₁-and H₂-receptor blockers.
30. 2. A method according to claim 1, wherein said nonsteroidal anti-inflammatory agent is aspirin or ibuprofen.
35. 3. A method according to either of claims 1 and 2 wherein said beta-adrenergic agonist is terbutaline or a pharmaceutically acceptable salt thereof and said histamine H₁-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof.
40. 4. A method according to any one of claims 1 to 3 comprising combining the ingredients in amounts which are sufficient to provide an average daily dose for the various ingredients as follows :
- (a) said nonsteroidal anti-inflammatory agent; from about 10 mg/kg/day to about 100 mg/kg/day,
 - (b) said beta-adrenergic agonist; from about 0.30 ug/kg/day to about 500 mg/kg/day,
 - (c) said histamine H₁-receptor blocker; from about 2.5 ug/kg/day to about 500 mg/kg/day.
45. 5. A method according to any one of claims 1 to 3 comprising combining the ingredients in amounts which are sufficient to provide an average daily dose for the various ingredients as follows:
- (a) said nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day,
 - (b) said beta-adrenergic agonist; from about 0.01 mg/kg/day to about 10 mg/kg/day;
 - (c) said histamine H₁-receptor blocker; from about 0.1 mg/kg/day to about 50 mg/kg/day.
50. 6. A method according to any one of claims 1 to 3 in which there is prepared a unit dosage form by combining the ingredients in the following amounts per unit dose:
- (a) said nonsteroidal anti-inflammatory agent; from about 200 mg to about 600 mg;
 - (b) said beta-adrenergic agonist; from about 0.7 mg to about 70 mg;
 - (c) said histamine H₁-receptor blocker; from about 0.01 mg to about 70 mg.
55. 7. A method according to either of claims 1 and 2 wherein said beta-adrenergic agonist is terbutaline or pharmaceutically acceptable salt thereof and said histamine H₂-receptor blocker is ranitidine or a pharmaceutically acceptable salt thereof.
8. A method according to any one of claims 1, 2 or 7 comprising combining the ingredients in amounts which are sufficient to provide an average daily dose for the various ingredients as follows:

(a) said nonsteroidal anti-inflammatory agent; from about 10 mg/kg/day to about 100 mg/kg/day,
(b) said beta-adrenergic agonist; from about 0.30 ug/kg/day to about 500 mg/kg/day,
(c) said histamine H₂-receptor blocker; from about 10ug/kg to about 1 g/kg/day.

5 9. A method according to any one of claims 1, 2 or 7 comprising combining the ingredients in amounts which are sufficient to provide an average daily dose for the various ingredients as follows :

(a) said nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day,
(b) said beta-adrenergic agonist; from about 0.01 mg/kg/day to about 10 mg/kg/day,
(c) said histamine H₂-receptor blocker; from about 0.01 mg/kg/day to about 10 mg/kg/day.

10 10. A method according to any one of claims 1, 2 or 7 which comprises preparing a unit dosage form by combining the ingredients in the following amounts per unit dose:

(a) said nonsteroidal anti-inflammatory agent; from about 200 mg to about 600 mg,
(b) said beta-adrenergic agonist; from about 0.7 mg to about 70 mg,
15 (c) said histamine H₂-receptor blocker; from about 0.5 mg to about 350 mg.

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EP 87 31 1170

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	EP-A-0 248 150 (BRISTOL-MYERS CO.) * Page 3, lines 29-33; page 11, lines 1-40 *	1-10	A 61 K 31/615 A 61 K 31/60 A 61 K 31/34
A	GB-A-2 105 193 (GLAXO GROUP LTD) * Page 3, lines 19-35 *	1-10	A 61 K 31/19 // (A 61 K 31/60 A 61 K 31:34
A	US-A-4 522 826 (RICHARDSON-VICKS INC.) * Column 11, line 60 - column 14, line 49 *	1-10	A 61 K 31:135) (A 61 K 31/34 A 61 K 31:19 A 61 K 31:135) (A 61 K 31/19 A 61 K 31:135)

TECHNICAL FIELDS SEARCHED (Int. Cl.4)			
A 61 K			
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 31-08-1988	Examiner BRINKMANN C.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
EPO FORM 1503/02.82 (P0001)			